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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,840	01/20/2006	Fabrizio Samaritani	7541-6	4228
30565 7590 07/20/2007 WOODARD, EMHARDT, MORIARTY, MCNETT & HENRY LLP 111 MONUMENT CIRCLE, SUITE 3700 INDIANAPOLIS, IN 46204-5137			EXAMINER KHANNA, HEMANT	
			ART UNIT 1654	PAPER NUMBER
			MAIL DATE 07/20/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/551,840	<b>Applicant(s)</b> SAMARITANI ET AL.	
	<b>Examiner</b> Hemant Khanna	<b>Art Unit</b> 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 May 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 46-89 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 72-74 is/are allowed.
- 6) ☒ Claim(s) 46-71 and 75-89 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>05/07/2007</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. This office action is in response to Applicant's remarks filed May 01, 2007.

Acknowledgement is made of amendments to claims 72-74 that make the said claims independent in order to overcome the Examiner's objection for being dependent on a rejected base claim.

2. Claims 46-89 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

### ***Claim Rejections - 35 USC § 103***

4. (Maintained) Claims 46-50, 57-60, 63-64, under 35 U.S.C. 103(a) as being unpatentable over Skrabanja et al (USPN 5,929,028) in view of Koll et al (USPN 6,346,274) is maintained for reasons set forth in the previous office action and for reasons set forth below.

Instant Claims are drawn to a liquid pharmaceutical composition comprising follicle stimulating hormone, a diluent and one surfactant selected from the group consisting of Pluronic F68, further comprising sucrose and methionine.

Applicant's argue that it would not have been obvious to interchange a surfactant from Koll with a surfactant disclosed in Skrabanja to arrive at the instant invention

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(Remarks, page 25, paragraph 2). Applicant's argue that Koll cannot be said to teach the combination of F68 specifically with FSH, because of Kolls recitation of a laundry list of additives and the disclosure of EPO in the examples. Applicant's argue that one skilled in the art would not even know from Koll whether Pluronic F68 had any advantageous effects over Tween 20 or Pluronic F127 with respect to the combination with EPO (Page 26, last paragraph). Applicant's argue that Pluronic F123 on one hand has very different properties than Pluronic F68 (page 27, third paragraph), wherein Pluronic F68 is primarily made up of hydrophilic ethylene oxide and Pluronic F123 is made up of primarily hydrophobic propylene oxide.

Applicant's arguments have been considered but not found persuasive.

The Examiner argues that it would be prima facie obvious to interchange the surfactant Tween 20 of Skrabanja with Pluronic F68 of Koll in view of the combined teachings of Skrabanja and Koll and further in view of Applicant's admittance that Tween 20 and Pluronic F68 induce similar effects in preventing aggregation of proteins such as EPO or FSH which are encapsulated in microparticles. The Examiner also respectfully points out that patents are relevant as prior art for all they contain, including the disclosure of alternatives.

MPEP 2123 (I) states "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments". MPEP 2123 (II) states "Furthermore, the prior art's mere disclosure of

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more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed”.

The primary reference teaches a liquid composition of FSH with Pluronic F123 or Tween 20 as set forth below. The examples in the reference use Tween 20 as a surfactant representative of non-ionic surfactants in FSH preparations. Moreover, the reference discusses the reason for the inclusion of preferred nonionic surfactants, such as Pluronic F123 in gonadotropin preparations for the purposes of injectable liquid medicaments as exemplified by the disclosures “the formulation of the invention preferably also comprises one or more nonionic surfactants” (column 5, lines 15-17). The reference also states that the addition of above “anti-adsorption agents to the formulations of the invention is especially required when the formulations comprise a recombinant gonadotropin in low concentrations” (column 5, lines 20-22). The reference points to solving a problem in that “contrary to the state of the art, a preparation is provided which can be injected directly, i.e. without the necessity to reconstitute a dried product before use” (column 7, lines 5-10). The reference also states that the “liquid gonadotropin containing formulations of the invention may be stored in the liquid state at various temperatures for prolonged periods while retaining the biological activity and physical stability of gonadotropin” (column 6, lines 45-50).

The secondary reference of Koll discloses microparticles composed of encapsulated FSH in presence of Pluronic F68 or Tween 20 as set forth below. Koll teaches microparticles composed of hydrophilic ABA triblock copolymers further

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comprising additives that are intended to keep the aggregation of the active substance low, with the purpose that the polypeptide contained within the microoparticle is as intact as possible. The reference states that triglycerides and detergents such as Tween 20, Tween 80 and the genus of pluronic are suitable within the sense of the invention (column 4, lines 40). Further, the reference of Koll teaches preferred embodiments of polypeptides with molecular weight of up to 100,000, such as EPO, calcitonin, FSH etc. (column 5, lines 5-10, claim 6) with EPO representative of a particularly preferred embodiment (column 5, lines 5-10).

The Applicants state that the Koll reference does not teach the advantages of Pluronic F68 over Pluronic F127. The Examiner disagrees. The reference teaches that microparticles containing Pluronic F127 led to an increased occurrence of deformed microparticles (column 9, lines 20-22), as exemplified in Table 2, with the inclusion of Pluronic F127 leading to an increased aggregation of EPO. Based on the above evidence, one of ordinary skill would have the incentive to prepare microparticle formulations of FSH with Pluronic F68 or Tween 20.

The Applicant's state that Pluronic F123 of Skrabanja has different properties than Pluronic F68 of Koll. Whether or not Pluronic F123 and Pluronic F68 have different properties is moot. Pluronic F68 of Koll is NOT being used interchangeably with Pluronic F123 of Skrabanja. Moreover, while the Applicant has admitted that the structural formulas of the two above-mentioned Pluronic species are different, the Applicant has not provided any evidence corroborating their arguments for differential properties. However, the Examiner submits that the properties of Pluronic F127 and

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Pluronic F68 are different as corroborated by the findings of Koll who explicitly teach the inclusion of Pluronic F127 led to an increased occurrence of deformed microparticles (see above). Further, in view of Koll and in view of Applicant's admittance, Tween 20 and Pluronic F68 are interchangeable over one another, since both reduce aggregation in EPO-PLGA microparticles to the same extent.

It would have been obvious to one of ordinary skill in the art to substitute Tween 20 of Skrabanja with Pluronic F68 of Koll to yield a liquid pharmaceutical composition of FSH and Pluronic F68. One would have been motivated to do so because the inclusion of Pluronic F68 would preclude both the aggregation of FSH in concentrated aqueous formulations for injectable use, and would preclude the loss of FSH by adsorption to vessel surfaces during storage of dilute aqueous formulations, both being recognized as problems in the pharmaceutical industry (Skrabanja, column 2, lines 20-25).

Claims 51-56, 61-62, 79-81, and 86-87 depend on the claims discussed above, and are submitted to be obvious for all the same reasons.

Rejection is maintained.

***Allowable Subject Matter***

5. Claims 72-74 are free of the prior art.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hemant Khanna whose telephone number is (571) 272-9045. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should



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you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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July 13, 2007



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